Analysis
As of: Feb 25, 2009

SANOFI-SYNTHELABO, SANOFI-SYNTHELABO, INC., and BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP, Plaintiffs-Appellees, v. APOTEX, INC. and APOTEX CORP., Defendants-Appellants.

2007-1438

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

550 F.3d 1075; 2008 U.S. App. LEXIS 24991; 89 U.S.P.Q.2D (BNA) 1370

December 12, 2008, Decided

PRIOR HISTORY: [**1]

Appeal from the United States District Court for the Southern District of New York in case no. 02-CV-2255, Judge Sidney H. Stein.
Sanofi-Synthelabo v. Apotex, Inc., 492 F. Supp. 2d 353, 2007 U.S. Dist. LEXIS 44033 (S.D.N.Y., 2007)

DISPOSITION: AFFIRMED.

CASE SUMMARY:

PROCEDURAL POSTURE: Plaintiff pharmaceutical companies sued defendant drug manufacturers, alleging that the manufacturers infringed *U.S. Patent No. 4,847,265 (the '265 patent)* when they filed an Abbreviated New Drug Application (ANDA) for Food and Drug Administration (FDA) approval to sell clopidogrel bisulfate. The U.S. District Court for the Southern District of New York found that claim 3 of the *'265 patent* was valid, and the manufacturers appealed.

OVERVIEW: The drug manufacturers filed an ANDA in November 2001, seeking FDA approval to sell clopidogrel bisulfate, a drug that inhibited the aggregation of blood platelets and was used to treat or prevent blood-thrombotic events such as heart attacks and strokes. Although the manufacturers admitted that their ANDA infringed the pharmaceutical companies' *'265 patent*, they stated, pursuant to *21 U.S.C.S. § 355(j)(2)(A)(vii)(IV)*, that they believed the *'265 patent* was invalid. The pharmaceutical companies filed suit for patent infringement, and when the parties failed to resolve the issues raised by the pharmaceutical companies' complaint and the drug manufacturers' counterclaims, the case was tried to the district court. The court of appeals found that the district court did not commit clear error when it found that claim 3 of the *'265 patent* was not invalid because it was obvious and anticipated by prior art. Although it was generally known that enantiomers could exhibit different biological activity, that degree and kind of stereoselectivity was rare, and the results the pharmaceutical companies achieved while conducting experiments could not have been predicted.

OUTCOME: The court of appeals affirmed the district court's ruling that claim 3 of the *'265 patent* was valid

and enforceable.

LexisNexis(R) Headnotes

Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

[HN1] Federal approval of a generic counterpart of a previously approved drug pursuant to an Abbreviated New Drug Application requires showing that the generic product is the same as the approved product. Evidence of safety and efficacy of the generic product is not required. *21 U.S.C.S. § 355(j)(2)(A)* and *(b)(1)*.

Civil Procedure > Appeals > Standards of Review > Clearly Erroneous Review

Patent Law > Anticipation & Novelty > Fact & Law Issues

Patent Law > Anticipation & Novelty > Knowledge & Use

Patent Law > Claims & Specifications > Enablement Requirement > General Overview

[HN2] Claimed subject matter is "anticipated" when it is not new; that is, when it was previously known. Invalidation on this ground requires that every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in possession of the invention. An anticipating reference must be enabling; that is, the description must be such that a person of ordinary skill in the field of the invention can practice the subject matter based on the reference, without undue experimentation. Anticipation is a question of fact, and a federal district court's finding of that issue is reviewed for clear error.

Patent Law > Anticipation & Novelty > Description in Patents

Patent Law > Anticipation & Novelty > Description in Publications

[HN3] To anticipate, a reference must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements arranged as in the claim. The reference must clearly and unequivocally disclose the claimed invention or direct those skilled in the art to the invention without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.

Patent Law > Anticipation & Novelty > Elements

[HN4] Any presumption of enablement of prior art does not exclude consideration of whether undue experimentation would be required to achieve enablement. The factors relevant to whether experimentation is undue include the quantity of experimentation that was actually needed, the amount of guidance provided in the reference, the presence or absence of actual examples of the experimental procedure, the state of the knowledge already available concerning the subject matter at issue, and the predictability or unpredictability in the specific area of science or technology.

Patent Law > Nonobviousness > Elements & Tests > Prior Art

Patent Law > Nonobviousness > Elements & Tests > Secondary Considerations

Patent Law > Nonobviousness > Evidence & Procedure > Fact & Law Issues

[HN5] The determination of obviousness is a matter of law based on findings of underlying fact, wherein the factors identified by the United States Supreme Court in Graham v. John Deere Co. guide the inquiry. Under *35 U.S.C.S. § 103*, the scope and content of the prior art are to be determined, differences between the prior art and the claims at issue are to be ascertained, and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim. For chemical compounds, the structure of the compound and its properties are inseparable considerations in the obviousness determination.

Patent Law > Nonobviousness > Evidence & Procedure > Presumptions & Proof

Patent Law > Nonobviousness > Evidence & Procedure > Prima Facie Obviousness

[HN6] Precedent establishes the analytical procedure

whereby a close structural similarity between a new chemical compound and prior art compounds is generally deemed to create a prima facie case of obviousness, shifting to the patentee the burden of coming forward with evidence of nonobviousness. The evidence may take various forms, as relevant in the particular case. The ultimate determination is made in the context of the factors the United States Supreme Court identified in Graham v. John Deere Co., with the challenger having the ultimate burden of proving invalidity by clear and convincing evidence.

Patent Law > Nonobviousness > Elements & Tests > Hindsight
Patent Law > Nonobviousness > Elements & Tests > Prior Art
Patent Law > Nonobviousness > Evidence & Procedure > Presumptions & Proof
[HN7] In Graham v. John Deere Co. the United States Supreme Court cautioned against the use of hindsight whereby the teachings of an invention are read into the prior art. In KSR v. Teleflex, the Court recognized "hindsight bias" and "ex post reasoning" as inappropriate in a determination of obviousness.

Patent Law > Nonobviousness > Elements & Tests > General Overview
[HN8] The determination of obviousness is dependent on the facts of each case.

COUNSEL: Evan R. Chesler, Cravath, Swaine & Moore LLP, of New York, New York, argued for plaintiffs-appellees. With him on the brief were Richard J. Stark and David Greenwald. Of counsel on the brief were Robert L. Baechtold, John D. Murnane, and William E. Solander, Fitzpatrick, Cella, Harper & Scinto, of New York, New York.

Robert B. Breisblatt, Welsh & Katz, Ltd., of Chicago, Illinois, argued for defendants-appellants. With him on the brief were Steven E. Feldman, Philip D. Segrest, Jr., and Sherry L. Rollo. Of counsel on the brief were Robert S. Silver, Manny D. Pokotilow, Bruce J. Chasan, and Mona Gupta, Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd., of Philadelphia, Pennsylvania.

JUDGES: Before NEWMAN, LOURIE, and BRYSON, Circuit Judges.

OPINION BY: NEWMAN

OPINION

[*1077] NEWMAN, Circuit Judge.

This suit arose in accordance with the provisions of the Hatch-Waxman Act, codified at *35 U.S.C. §271 (e)* and *21 U.S.C. §355(j)*. The patent at issue is *United States Patent No. 4,847,265 (the '265 patent)*, owned by Sanofi-Synthelabo and related companies (collectively "Sanofi"), and covers the [**2] pharmaceutical product having the common name clopidogrel bisulfate and the brand name Plavix(R). The product has the property of inhibiting the aggregation of blood platelets, and is used to treat or prevent blood-thrombotic events such as heart attacks and strokes. We affirm the district court's ruling sustaining patent validity.

BACKGROUND

Clopidogrel is the common name of the dextrorotatory isomer of the chemical compound named methyl
alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)
-acetate. Claim 3 of the patent is in suit:

> 3. Hydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-a substantially separated from the levo-rotatory isomer.

The *'265 patent* was issued on July 11, 1989, with priority from an application first filed in France in 1987. Approval of the product by the United States Food and Drug Administration (FDA) was received in 1998.

[*1078] Apotex, Inc. filed an Abbreviated New Drug Application (ANDA) [1] in November 2001 for FDA approval to sell clopidogrel bisulfate, stating, pursuant to *21 U.S.C. §355(j)(2)(A)(vii)(IV)*, that it believed the *'265 patent* to be invalid. Such "paragraph IV certification" [**3] is defined as an act of infringement for litigation purposes, *35 U.S.C. §271 (e)*, in order to facilitate pre-marketing legal challenge by the producer of a generic form of a patented pharmaceutical product. In accordance with the statutory procedures Sanofi duly filed suit for infringement, and Apotex counterclaimed that the *'265 patent* is invalid on several grounds and unenforceable. The suit initiated a thirty-month stay of

FDA approval of Apotex's ANDA, as provided by *21 U.S.C. §355(j)(5)(B)(iii)*. A proposed settlement was not achieved, the statutory stay expired, the FDA approved the Apotex ANDA, and Apotex commenced sale of its generic clopidogrel bisulfate product on August 8, 2006. Sanofi then moved in the district court for a preliminary injunction, asking that Apotex be enjoined from marketing its infringing product while the litigation was pending, noting that infringement was conceded by Apotex.

> 1 [HN1] Federal approval of a generic counterpart of a previously approved drug pursuant to an ANDA requires showing that the generic product is the same as the approved product; evidence of safety and efficacy of the generic product is not required. See *21 U.S.C. §§355(j)(2)(A)* and *355(b)(1)*.

The [**4] district court found that Sanofi was likely to succeed on the merits of the validity and enforceability of the *'265 patent*, and that the equitable factors of the balance of harms, the probability of irreparable harm, and the various public interests, favored granting the injunction. *Sanofi-Synthelabo v. Apotex Inc., 488 F. Supp. 2d 317, 350 (S.D.N.Y. 2006)* ("Sanofi I"). This court affirmed the district court's rulings, while explaining that the record on the substantive issues was necessarily incomplete and that the district court could review all aspects at trial. See *Sanofi-Synthelabo v. Apotex Inc., 470 F.3d 1368, 1374-84 (Fed. Cir. 2006)* ("Sanofi II") (holding that the patentee was likely to succeed on the merits, and that the balance of hardships and public interest supported the injunction). A bench trial was held from January 22 to February 15, 2007, following which the district court ruled that the *'265 patent* is valid and enforceable. *Sanofi-Synthelabo v. Apotex Inc., 492 F. Supp. 2d 353, 397 (S.D.N.Y. 2007)* ("Sanofi III").

This appeal is focused on the question of patentability of this dextrorotatory isomer in view of its known racemate described in earlier Sanofi patents, [**5] specifically, Sanofi's *United States Patent No. 4,529,596 (the '596 patent)* and Canadian *Patent No. 1,194,875 (the '875 patent)*. Both reference patents are derived from the same French priority filing and are prior art against the *'265 patent*.

The activities that led to the product in suit are discussed in the earlier opinions, and are summarized as relevant herein: In 1972 Sanofi scientists were seeking products that might have improved anti-inflammatory properties, and in the course of this work discovered that certain compounds of the class known as thienopyridines (compounds having a thiene ring fused to a pyridine ring) have the property of inhibiting blood platelet aggregation. Sanofi scientists, led by Dr. Jean-Pierre Maffrand, pursued this direction of research. The record states that they initially synthesized and evaluated several hundred chemical modifications and derivatives of thienopyridines, seeking optimum anti-platelet aggregation properties with [*1079] minimal undesirable effects. They eventually selected for development the compound having the following structural formula:

[SEE FIGURE IN ORIGINAL]

Sanofi gave this compound the common name "ticlopidine." After lengthy development, [**6] including animal and human trials, in 1991 ticlopidine was approved in the United States for use as an anti-thrombotic agent. This approval, however, was accompanied by required warnings concerning possible adverse effects, for reports had been received of rarely occurring but serious blood disorders, neutropenia and thrombotic thrombocytopenic purpura, associated with prolonged usage of ticlopidine. Thus Sanofi continued its search for a product that would have the therapeutic benefits of ticlopidine but without the adverse properties.

Sanofi synthesized and evaluated several hundred additional thienopyridine derivatives, including a class of compounds having the following general structure, wherein one of the hydrogen atoms on the bridge carbon atom (marked with an asterisk), is replaced with an ester, carboxylic acid, or amide group. This class is the subject of the *'596 patent* (and the counterpart Canadian *'875 patent*), and is shown as follows:

[SEE FIGURE IN ORIGINAL]

X and Y can be any of a number of substituents, as identified in the patents; the district court found that there are thirty-seven possibilities for X and 1710 choices for Y. The patents state that compounds of this [**7] class exhibit good anti-platelet aggregation properties and are well tolerated. Focusing on the *'596 patent*, the specification includes twenty-one examples of specific compounds, including a compound designated as PCR 4099, which Sanofi synthesized in July 1980. In PCR

4099 the substituent attached to the bridge carbon is the methyl ester group (-COOCH[3]), and X is chlorine in the 2-position, as follows:

[SEE FIGURE IN ORIGINAL]

[*1080] This compound has the chemical name methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl)(2-chlorophenyl)-acetate, with the acronym MATTPCA. PCR 4099 as the hydrochloride salt was selected for commercial development as a potential replacement for ticlopidine in light of its improved platelet inhibition and toxicity profile.

However, PCR 4099 still raised toxicity concerns, for at very high doses it caused convulsions in laboratory animals. Thus the research efforts continued, concurrently with the clinical and commercial development of PCR 4099. Sanofi states that about 1500 compounds in this general class were synthesized, of which about 600, including PCR 4099, were chiral thienopyridines. "Chiral" is defined as "describ[ing] asymmetric molecules that are [**8] mirror images of each other, i.e., they are related like right and left hands. Such molecules are also called enantiomers and are characterized by optical activity." Richard J. Lewis, Sr., Hawley's Condensed Chemical Dictionary 270 (15th ed. 2007).

Enantiomers are spatial isomers, also called stereoisomers, wherein the isomeric compounds have the same chemical formula and the same chemical structure, but differ in their orientation in three-dimensional space. Such stereoisomers can exist for all molecules that contain an asymmetric carbon atom. An "asymmetric carbon" is a carbon atom to which four different substituents are attached, whereby, due to the tetrahedral structure of carbon bonds in three dimensions, the spatial orientation of substituents attached to a carbon atom varies. When there is only one asymmetric carbon atom in the molecule and thus only two stereoisomers, these isomers are called enantiomers.

Enantiomers are identified and distinguished by their optical characteristics when a purified solution of the separated isomers is exposed to plane-polarized light. One enantiomer will rotate plane-polarized light to the right (and thus is called the dextrorotatory or *d*- or [**9] (+) isomer), and the other rotates plane-polarized light to the left (called the levorotatory or *l*- or (-) isomer). For the compounds here at issue, the asymmetric carbon is at the bridge between the thienopyridine and the benzene components of the molecule, as marked with an asterisk in the drawings shown ante. Enantiomers generally are formed in equal amounts, to produce what is called a racemate; the racemate is optically neutral.

In the district court, experts for both sides explained the difficulty of separating enantiomers, for they are identical except for the spatial arrangement at one of the carbon atoms. Sanofi scientists had previously separated the enantiomers of two thienopyridines, and had found that the separated enantiomers showed no advantage over the racemates. The first such separation was conducted in 1978 for a [*1081] compound designated PCR 1033, which had a methyl group in place of one of the hydrogen atoms on the bridge carbon of ticlopidine, and whose maleate salt was found to be more potent than ticlopidine in antiplatelet activity but had undesirable side effects. On separation, it was found that one of the enantiomers of PCR 1033 was more biologically active but [**10] also more neurotoxic than the racemate. Thus, separation offered no benefit for PCR 1033.

About three years later, Sanofi separated the enantiomers of a compound designated PCR 3233, which had an ethyl group on the bridge carbon, and was more effective in antiplatelet activity than ticlopidine. However, neither of the separated enantiomers differed in activity from the racemate, and thus separation offered no benefit for PCR 3233. Sanofi witnesses testified to their belief that there was no advantage to separation of the enantiomers of thienopyridines, and no other racemates were separated until, in November 1985, Dr. Maffrand decided to study the enantiomers of PCR 4099.

The separation for PCR 4099 was assigned to Mr. Alain Badorc, the chemist who had separated the enantiomers of PCR 1033 and 3233. It was explained in the district court that such separations are complex and time-consuming, for enantiomers are identical except for the spatial orientation about one carbon atom, and tend to have identical or almost identical chemical and physical properties. The district court received testimony that although the chemical literature shows at least ten separation techniques that might be [**11] tried, it cannot be known in advance which, if any, technique might work.

The record shows five months of experimentation by Mr. Badorc, and eventually the successful separation using a technique called diastereomeric salt formation.

This procedure, which originated with Louis Pasteur, is based on the trial of diverse salt-forming compositions and conditions, in the hope of coming upon a lucky combination of reagents that will preferentially select one of the enantiomers and crystallize from the solution in optically pure form. In Mr. Badorc's successful experiment, he prepared thirty compositions of PCR 4099 and various resolving acids at various concentrations and in various solvents, and after about one month crystals formed in the composition containing (+)camphorsulfonic acid and PCR 4099 in a 4:10 ratio, dissolved in acetone. This combination eventually yielded the pure levorotatory enantiomer, and isolation of the pure dextrorotatory enantiomer followed, as discussed by the district court in *Sanofi III, 492 F. Supp. 2d at 372-73*.

Sanofi then determined the biological properties of the enantiomers of PCR 4099, and found that they had the rare characteristic of "absolute [**12] stereoselectivity": the dextrorotatory enantiomer provided all of the favorable antiplatelet activity but with no significant neurotoxicity, while the levorotatory enantiomer produced no antiplatelet activity but virtually all of the neurotoxicity. The experts for both sides agreed that while it was generally known that enantiomers can exhibit different biological activity, this degree and kind of stereoselectivity is rare, and could not have been predicted. The experts explained that in the usual case, if one enantiomer is more biologically active than the other, that activity includes the adverse as well as the beneficial properties.

In view of these results, in April 1987 Sanofi terminated commercial development of the racemate PCR 4099, which had been proceeding since 1980 and had reached Phase I human trials at a cost stated to be tens of millions of dollars. More years of development ensued for the dextrorotatory enantiomer, to which Sanofi gave the common [*1082] name "clopidogrel." Sanofi also found that the hydrochloride salt, which had been suitable for processing and tabletting the racemate PRC 4099, was not suitable for clopidogrel. After further research, Sanofi found that the [**13] hydrogen sulfate salt (also called the bisulfate) was suitable for tabletting. FDA approval of clopidogrel bisulfate was achieved in the United States in 1998, allowing introduction of the product Plavix(R).

Sanofi filed a patent application directed to clopidogrel and certain salts and pharmaceutical compositions, in France on February 17, 1987 and then in the United States and other countries. The United States patent is the *'265 patent* in suit. The *'265 specification* explains that the racemate of the same chemical formula was described in the earlier French *'247 patent*, which corresponds to the earlier U.S. *'596 patent*. The *'265 patent* discusses the unusual stereoselectivity of the biological properties as between the dextrorotatory and the levorotatory enantiomers. The United States patent examiner, who had also examined the *'596 patent*, allowed the claims after requiring that the '265 claims make clear that the dextro- and levo- enantiomers are "substantially separated."

Apotex stipulated that claim 3 of the *'265 patent* is literally infringed by its product. The district court, after full trial including extensive expert testimony provided by both sides, ruled that claim 3 is valid [**14] and enforceable. Apotex appeals the court's rulings on the issues of anticipation and obviousness; the rulings in Sanofi's favor on the issues of unenforceability and double patenting are not appealed.

ANTICIPATION

[HN2] Claimed subject matter is "anticipated" when it is not new; that is, when it was previously known. Invalidation on this ground requires that every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in possession of the invention. See *Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1379 (Fed. Cir. 2003)*; *Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1267-69 (Fed. Cir. 1991)*. An anticipating reference must be enabling; that is, the description must be such that a person of ordinary skill in the field of the invention can practice the subject matter based on the reference, without undue experimentation. See *Amgen Inc. v. Hoechst Marion Roussel, Inc., 457 F.3d 1293, 1306-07 (Fed. Cir. 2006)*; *Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Research, 346 F.3d 1051, 1054 (Fed. Cir. 2003)*. Anticipation is a question of fact, and the district court's [**15] finding of this issue is reviewed for clear error. See *Merck & Co. v. Teva Pharms. USA, Inc., 347 F.3d 1367, 1369 (Fed. Cir. 2003)*.

A

The district court identified the limitations stated in claim 3 of the *'265 patent* as (1) the bisulfate salt of (2)

the dextrorotatory enantiomer of (3) the compound MATTPCA (4) substantially separated from the levorotatory enantiomer. The references on which Apotex relied were the *'596 patent* or its Canadian '875 counterpart. Apotex argued that either reference not only shows the racemate PCR 4099, but also its addition salts and enantiomeric forms. The district court discussed that these references show PCR 4099 only as the racemate, and do not show the separated enantiomer or the bisulfate salt thereof. The district court found that although the racemate is in the prior art, the dextrorotatory enantiomer and salt in claim 3 of the *'265 patent* are [*1083] not described, either explicitly or inherently, in any reference.

The court heard expert witnesses for both sides, who agreed that persons of ordinary skill in this field would have known that compounds that contain an asymmetric carbon atom have enantiomers. The *'596 specification* states: "These compounds having [**16] an asymmetrical carbon may exist in the form of two enantiomers. The invention relates both to each enantiomer and their mixture." *'596 patent*, col. 1, lines 39-41. However, as the witnesses agreed, all of the compounds in the *'596 patent* are racemates, and neither the twenty-one specific examples nor any other part of the specification shows their separation into enantiomers. The district court reasoned that a person of ordinary skill in the field of the invention would not have been guided to either the dextrorotatory enantiomer of PCR 4099 or its bisulfate salt.

Apotex argues that the district court erred in law, and that it suffices that the reference shows the specific racemate PCR 4099 and states that the compounds in the reference have enantiomers and that the enantiomers are included in the invention. Apotex states that the separation of enantiomers is routine, even if time-consuming or requiring some experimentation, and thus that that the separation need not have been performed or described in the reference. Apotex states that the properties of the enantiomers of PCR 4099 are inherently and necessarily present in its known racemate, such that when the enantiomers are separated [**17] the previously observed properties are "immediately recognized" in one or the other enantiomer.

Apotex stresses that the *'596 patent*'s Example 1 is specific to PCR 4099, and the '596 claims refer to "addition salts with pharmaceutically acceptable mineral or organic acids" and "both enantiomeric forms or their mixture." The counterpart Canadian *'875 patent* states that when the desired structure is obtained it "is isolated and, if desired, its enantiomers are separated and/or it is salified by mineral or organic acid action." Apotex concedes that the references do not show any separated enantiomers or describe how to separate them, but argues that such detail is not required because persons of ordinary skill would know the existing techniques for separating enantiomers. Apotex thus argues that the dextrorotatory enantiomer of MATTPCA cannot be deemed novel, as a matter of law. However, as the district court recognized, that is not the correct view of the law of anticipation, which requires the specific description as well as enablement of the subject matter at issue. [HN3] To anticipate, the reference "must not only disclose all elements of the claim within the four corners of the document, [**18] but must also disclose those elements 'arranged as in the claim.'" *Net MoneyIN, Inc. v. VeriSign, Inc., 545 F.3d 1359, 1369 (Fed. Cir. 2008)* (quoting *Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1548 (Fed. Cir. 1983)*); see also, e.g., *In re Arkley, 455 F.2d 586, 587, 59 C.C.P.A. 804 (CCPA 1972)* ("[The] reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference" (emphasis in original)).

The district court analyzed the question as whether a generic disclosure necessarily anticipates everything within the genus, and recognized that the answer depends on the factual aspects of the specific disclosure and the particular products at issue. See, e.g., *Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006)* ("It [*1084] is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus."). In *In re Ruschig, 343 F.2d 965, 974, 52 C.C.P.A. 1238, 1965 Dec. Comm'r Pat. 482 (CCPA 1965)*, the court declined to find the disclosed genus anticipatory of everything [**19] within its scope, when the description of the genus would not lead a person of ordinary skill to a "small recognizable class with common properties." In this case the district court correctly declined to find that the references' general statements that these compounds consist of enantiomers constituted an anticipating disclosure of the separated dextrorotatory enantiomer of PCR 4099.

The district court discussed the cases on which Apotex particularly relied: *In re Petering, 301 F.2d 676, 49 C.C.P.A. 993, 1962 Dec. Comm'r Pat. 232 (CCPA 1962)*, and *In re Schaumann, 572 F.2d 312 (CCPA 1978)*. The court pointed out that in Petering and Schaumann the generic disclosure in the reference identified "specific preferences," [**20] which were met by the later-described species. We discern no clear error in the district court's finding that the references herein contained no such specific preferences. PCR 4099 is shown in the references as one of several compounds with desirable biological properties, but the district court did not clearly err in finding that the reference disclosure would not have led one of ordinary skill to recognize either an explicit or an inherent disclosure of its dextrorotatory enantiomer, as well as the bisulfate salt.

Apotex also relies on *In re Adamson, 275 F.2d 952, 47 C.C.P.A. 839, 1960 Dec. Comm'r Pat. 177 (CCPA 1960)*, where the court held that although the reference did not state that the disclosed compound was a racemate, it would have been known to one of ordinary skill that synthetically produced chiral compounds are racemic. Sanofi does not dispute this statement of stereochemistry, but points out that knowledge of the existence of enantiomers is not a description of a specific enantiomer "substantially separated" from the other, as in claim 3 of the *'265 patent*. The district court cited *In re May, 574 F.2d 1082 (CCPA 1978)*, which is explicit that "the novelty of an optical isomer is not negated by the prior art disclosure [**21] of its racemate." *Id. at 1090*. Also, Adamson and May were addressing rejections for obviousness, and neither case stated or suggested a previously unseparated and unknown enantiomer might be deemed anticipated by the known racemate.

The district court did not clearly err in finding that the statements in the *'596 patent* and its Canadian counterpart that the products therein consist of enantiomers are not a description of the specific dextrorotatory enantiomer clopidogrel or a suggestion of its unusual stereospecific properties. The knowledge that enantiomers may be separated is not "anticipation" of a specific enantiomer that has not been separated, identified, and characterized. The district court correctly held that neither the *'596 patent* nor its Canadian counterpart contains an anticipating disclosure of the subject matter of claim 3 of the *'265 patent*.

B

The parties also debated the question of enablement with respect to anticipation. The district court found that the asserted references are not enabling, for they contain no guidance as to how to separate the enantiomers of PCR 4099. Based on the evidence adduced at trial, the court concluded that absent such guidance, undue experimentation [**22] would be required.

Apotex argues that it is entitled to a presumption of enablement because the asserted references are patents, which are presumed to be enabling because they are presumed valid, citing *Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1355* [*1085] *(Fed. Cir. 2003)* ("We hold that an accused infringer should be similarly entitled to have the district court presume the enablement of unclaimed (and claimed) material in a prior art patent defendant asserts against a plaintiff."). Apotex [**23] argues that the presumption should be particularly strong here, because the prior art patents belong to Sanofi. Thus Apotex argues that the general statements in the reference patents concerning enantiomers are presumptively enabling of the separate enantiomers of PCR 4099. Apotex states that it is irrelevant whether the separation of this specific enantiomer is shown in the references, because a person of ordinary skill in this field would know all of the existing techniques for separating stereoisomers, and would presumptively succeed in this particular separation. Apotex points out that the method that was eventually used by Sanofi was a well-known method, even if it involved some experimentation.

[HN4] Any presumption of enablement of prior art does not exclude consideration of whether undue experimentation would be required to achieve enablement. See, e.g., *Elan Pharms, 346 F.3d at 1054* (the reference must teach how to carry out the invention without undue experimentation). The factors relevant to whether experimentation is undue are discussed in, e.g., *In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988)*, and include the quantity of experimentation that was actually needed, the amount of [**24] guidance provided in the reference, the presence or absence of actual examples of the experimental procedure, the state of the knowledge already available concerning the subject matter at issue, and the predictability or unpredictability in the specific area of science or technology. The *'596 patent* reference states only that "if desired, its enantiomers are separated," and similarly for the Canadian counterpart. The district court found that these references contain no description

of how to separate the enantiomers of PCR 4099, and that "[d]iscovering which method and what combination of variables is required is sufficiently arduous and uncertain as to require undue experimentation, even by one skilled in the relevant art." *Sanofi III, 492 F. Supp. 2d at 387.* This finding has not been shown to be clearly erroneous. In *Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc., 501 F.3d 1263 (Fed. Cir. 2007)*, this court recognized the known difficulty of separating enantiomers and the unpredictability of their properties, and held that a reference that stated that a compound has enantiomers did not enable the separation of those enantiomers, where the reference did not teach how to obtain [**25] the enantiomer. *Id. at 1268-69.* We discern no clear error in the district court's finding herein that the reference patents would not have enabled a person of ordinary skill to obtain clopidogrel substantially separated from the levorotatory enantiomer.

The district court's ruling that claim 3 of the *'265 patent* is not invalid for anticipation is affirmed.

OBVIOUSNESS

[HN5] The determination of obviousness is a matter of law based on findings of underlying fact, wherein the factors identified in *Graham v. John Deere Co., 383 U.S. 1, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966)*, guide the inquiry:

> Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations [*1086] as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

Id. at 17-18.

The determination of obviousness is made with respect to the subject matter as a whole, not [**26] separate pieces of the claim. See *KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 127 S. Ct. 1727, 1734, 167 L. Ed. 2d 705 (2007)*; *Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d 1437, 1448 (Fed. Cir. 1984).* For chemical compounds, the structure of the compound and its properties are inseparable considerations in the obviousness determination. See *In re Sullivan, 498 F.3d 1345, 1353 (Fed. Cir. 2007)*; *In re Papesch, 315 F.2d 381, 391, 50 C.C.P.A. 1084, 1963 Dec. Comm'r Pat. 334 (CCPA 1963).* [HN6] Precedent establishes the analytical procedure whereby a close structural similarity between a new chemical compound and prior art compounds is generally deemed to create a prima facie case of obviousness, shifting to the patentee the burden of coming forward with evidence of nonobviousness. The evidence may take various forms, as relevant in the particular case. See, e.g., *Takeda Chem. Industries, Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1358, 1362-63 (Fed. Cir. 2007)* (prima facie case depends on whether the prior art provided a suggestion or reason to choose a specific lead compound for modification, or to make the specific modification of the compound at issue); *Eisai Co. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1359 (Fed. Cir. 2008)* (same). The ultimate determination [**27] is made in the context of the Graham factors, with the challenger having the ultimate burden of proving invalidity by clear and convincing evidence. See *Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1360 (Fed. Cir. 2007).*

The district court assumed that Apotex had made a prima facie case of obviousness based on the reference patents' disclosure of the PCR 4099 racemate, the statements in the patents concerning enantiomers, and the general knowledge that enantiomers may be separated and may differ from each other in biological properties. Upon consideration of the Graham factors, the court held that the unpredictable and unusual properties of the dextrorotatory enantiomer and the therapeutic advantages thereby provided, weighed in favor of nonobviousness, and that Apotex had not met its burden of establishing otherwise.

Apotex argues that the recognition in the prior art that PCR 4099 is composed of enantiomers outweighs the effect of any unexpected or unpredictable properties of the separated dextrorotatory enantiomer. Apotex asserts that Sanofi's previous selection of PCR 4099 as a promising replacement for ticlopidine would have led a skilled artisan to start with PCR 4099 as a lead [**28] compound for further research. Apotex states that it was well known that enantiomers can have different levels of

other known strategies for enantiomer separation. The court observed that although Sanofi had previously separated the enantiomers of two other thienopyridines, the diastereomeric salt formation method had succeeded in one case but failed in the other. The court also found that a person of ordinary skill would have recognized that it could be more difficult to separate the enantiomers of PCR 4099 than the two other compounds that Mr. Badorc had previously separated, because it would be understood by chemists that the methyl ester substituent in PCR 4099 could make it more susceptible to re-racemization, and thus resistant to successfully obtaining a separated product.

The district court found that this separation was not a simple or routine procedure and that success in separation, [**33] as well as the allocation of properties, was unpredictable. The court observed that Apotex did not cite any reference showing or suggesting any reliable method of separation for any analogous compounds. The court described the separation as a "paradigm of trial and error," *Sanofi III, 492 F. Supp. 2d at 370*, and found that "neither the chemists at Sanofi nor a person of ordinary skill in the art could have reasonably expected that the separate enantiomers of PCR 4099 could be obtained at the time that Sanofi was contemplating whether to investigate them and, if obtained, they could not have predicted by what method and configuration." *Id. at 371*. The court found that Sanofi's expenditure of tens of millions of dollars for several years of development of the racemate PCR 4099, before separating the enantiomers, also weighed against finding that separation would have been obvious. Again, Apotex has demonstrated no clear error in the extensive finding of the district court concerning the difficulty and unpredictability of the separation of these enantiomers. These unchallenged findings undermine Apotex's argument in this appeal that the separation of the enantiomers would have been obvious. [**34] Only with hindsight knowledge that the dextrorotatory enantiomer has highly desirable properties, can Apotex argue that it would have been obvious to select this particular racemate and undertake its arduous separation. The application of hindsight is inappropriate where the prior art does not suggest that this enantiomer could reasonably be expected to manifest the properties and advantages that were found for this particular dextrorotatory isomer. See [HN7] *Graham, 383 U.S. at 36* (cautioning against hindsight whereby the teachings of the invention are read into the prior art); see also *KSR v. Teleflex, 127 S. Ct. at 1742* (recognizing "hindsight bias" and "ex post reasoning" as inappropriate in determination of obviousness).

Concerning the bisulfate salt, the district court found no evidentiary support for Apotex's argument that the *'596 patent* taught the dextrorotatory enantiomer of PCR 4099 as the bisulfate salt. The PCR 4099 racemate is shown in the *'596 patent* as the hydrochloride, not the bisulfate. The district court observed that the scientific literature listed eighty acids as candidates for forming salts with basic drug [*1089] compounds, fifty-three of which acids had been used in FDA-approved [**35] drugs. The experts of both parties agreed that whether a pharmaceutically suitable crystalline salt will form from a particular acid-base combination is unpredictable. The district court distinguished the facts of this case from those of *Pfizer 480 F.3d 1348*, where there was evidence that based on the prior art a person of ordinary skill would have narrowed the possible salts to only a few including the claimed besylate, whereas here Sanofi presented evidence that the prior art taught away from the use of sulfuric acid with an enantiomer, for strong acids could encourage re-racemization. Apotex has shown no clear error in the district court's finding, based on the trial evidence, that the facts distinguish this case from those in Pfizer.

Based on all of these findings, the district court concluded: "Whether or not it may have been 'obvious to try' separating the enantiomers of PCR 4099 and, secondarily, preparing its dextrorotatory enantiomer as a bisulfate salt, the wide range of possible outcomes and the relative unlikelihood that the resulting compound would exhibit the maximal increase in antiplatelet aggregation activity and the absence of neurotoxicity makes clopidogrel bisulfate [**36] non-obvious." *Sanofi III, 492 F. Supp. 2d at 392*. Apotex argues that the district court applied an incorrect inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general knowledge that enantiomers can exhibit different properties. Apotex refers to *In re Adamson, 275 F.2d at 955, 47 C.C.P.A. 839, 1960 CCPA LEXIS 327*, where the CCPA held that an enantiomer would have been obvious in view of its racemate. However, the scientific facts differed from these herein, for in Adamson the court found that it was "particularly expected" that the specific enantiomer

would have the observed properties. In contrast, as Sanofi points out, in *In re May, 574 F.2d at 1095*, the CCPA held, as to the enantiomer claimed therein, that the appellant "established a substantial record of unpredictability vis-a-vis a highly significant combination of properties."

[HN8] The determination of obviousness is dependent on the facts of each case. See *Graham, 383 U.S. at 17-18*. In *Forest Laboratories, 501 F.3d at 1269*, this court affirmed that the (+) enantiomer of citalopram would not have been obvious in [**37] light of the known racemate, when it was shown that the therapeutic properties of the (+) enantiomer were unexpected. In contrast, in *Aventis Pharma Deutschland GmbH v. Lupin, Ltd. 499 F.3d 1293, 1302 (Fed. Cir. 2007)*, this court held that the ramipril isomer's potency was "precisely what one would expect, as compared to a mixture containing other, inert or near-inert stereoisomers." Apotex argues that Aventis is the closer analogy, but the evidence was directly contrary to that position. The district court entered extensive findings in this case on the unexpected and unpredictable properties of clopidogrel, and there was no contrary evidence suggesting, based on the prior art, that the stereoselective properties were "precisely what one would expect," as in Aventis.

Apotex also argued in the district court, and repeats on this appeal, that Sanofi separated the enantiomers only because of a possible future regulatory requirement concerning the separation of enantiomers. Apotex states that this future regulatory requirement would have alerted a person of ordinary skill to the need to separate isomers, and thus would have rendered it obvious to do so. The district court found that the [**38] sole evidence referring to this regulatory possibility, an internal Sanofi memorandum, was written [*1090] several months after Sanofi had discontinued its development of the racemic PCR 4099 in favor of the dextrorotatory enantiomer; the court also cited the testimony and documentary evidence that Sanofi undertook this separation in order to study the adverse neurological effects of PCR 4099, and not because of a possible future regulatory requirement. Sanofi also points out, as the general knowledge in this field confirms, that the recognition that stereoisomers may exhibit different properties does not teach which results may ensue or how to separate any given enantiomers. We discern no error in the short shrift that the district court gave to this argument.

Apotex also argues that the district court did not take adequate account of the Supreme Court's holding in KSR v. Teleflex that the "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *127 S. Ct. at 1739*. Apotex states that Sanofi did no more than separate the enantiomers and determine their properties, and that the properties were predictably those [**39] of the racemate, allocated between the enantiomers. Sanofi points out that this case does not concern a "combination of familiar elements" as in the KSR mechanical device made by combining known components to produce a combination having the properties of the known components. The evidence at trial well supported the finding that the result of this separation of enantiomers was unpredictable. We discern no error in the district court's implicit recognition that the principles of KSR do not affect the conclusion herein.

The district court thoroughly discussed the many issues and arguments raised by Apotex. We discern no error in the district court's findings that, on the state of the prior art, a person of ordinary skill would not have had the expectation that separating the enantiomers would be likely to produce an isomer having absolute stereoselectivity as to both the favorable antiplatelet activity and the unfavorable neurotoxicity. The totality of these findings, and the correct application of law, well support the district court's conclusion that invalidity had not been established by clear and convincing evidence.

AFFIRMED

STEDMAN'S Medical Dictionary

27th Edition

Illustrated in Color

and lentiform nuclei) suggest that d. may have other functions. Depletion of d. produces Parkinson *disease*. SYN 3-hydroxytyramine, decarboxylated dopa.

d. hydrochloride, a biogenic amine and neural transmitter substance, used as a vasopressor agent for treatment of shock.

do·pa·mine β-hy·drox·y·lase. SYN dopamine β-monooxygenase.

do·pa·mine β-mon·o·ox·y·gen·ase. A copper-containing enzyme catalyzing oxidation of ascorbate and 3,4-dihydroxyphenylethylamine simultaneously by O_2 to yield norepinephrine, dehydroascorbate, and water; a crucial step in catecholamine metabolism. The enzyme is stimulated by fumarate. SYN dopamine β-hydroxylase.

do·pa·min·er·gic (dō″pă-min-er′jik). Relating to nerve cells or fibers that employ dopamine as their neurotransmitter. [dopamine + G. *ergon*, work]

dope (dōp). **1.** Any drug, either stimulating or depressing, administered for its temporary effect, or taken habitually or addictively. **2.** To administer or take such a drug. [Dutch, *doop*, sauce]

dop·ing (dōp′ing). The administration of foreign substances to an individual; often used in reference to athletes who try to stimulate physical and psychological strength.

Doppler, Johann Christian, Austrian mathematician and physicist, 1803–1853. SEE D. *echocardiography*, *effect*, *phenomenon*, *shift*, *ultrasonography*.

Dop·pler. A diagnostic instrument that emits an ultrasonic beam into the body; the ultrasound reflected from moving structures changes its frequency (Doppler effect). Of diagnostic value in peripheral vascular and cardiac disease.

do·ra·pho·bia (dō-rā-fō′bē-ă). Morbid fear of touching the skin or fur of animals. [G. *dora*, hide, skin, + *phobos*, fear]

Dorello, P., Italian anatomist, *1872. SEE D. *canal*.

Dorendorf, H., German physician, *1866. SEE D. *sign*.

Dorfman, Maurice L., 20th century Israeli dermatologist. SEE D.-Chanarin *syndrome*.

Döring, G., 20th century German neurologist. SEE Pette-D. *disease*.

dor·nase (dōr′nās). Obsolete contraction of deoxyribonuclease. SEE ALSO streptodornase.

pancreatic d., a stabilized deoxyribonuclease preparation from beef pancreas; used by inhalation in the form of aerosols to reduce thick mucopurulent secretions in certain bronchopulmonary infections.

Dorno, Carl, Swiss climatologist, 1865–1942.

do·ro·ma·ni·a (dō-rō-mā′nē-ă). An abnormal desire to give presents. [G. *dōron*, gift, + *mania*, insanity]

dor·sa (dōr′să). Plural of dorsum.

dor·sab·dom·i·nal (dōr-sab-dom′i-nal). Relating to the back and the abdomen.

dor·sad (dor′sad). Toward or in the direction of the back. [L. *dorsum*, back, + *ad*, to]

dor·sal (dōr′săl) [TA]. **1.** Pertaining to the back or any dorsum. SYN tergal. **2.** SYN posterior (2). **3.** In veterinary anatomy, pertaining to the back or upper surface of an animal. Often used to indicate the position of one structure relative to another; i.e., nearer the back surface of the body. **4.** Old term meaning thoracic, in a limited sense; e.g., d. vertebrae. [Mediev. L. *dorsalis*, fr. *dorsum*, back]

dor·sa·lis (dōr-sā′lis) [TA]. SYN posterior (2). [L.]

Dorset, Marion, U.S. bacteriologist, 1872–1935. SEE D. culture egg *medium*.

dor·si·duct (dōr′si-dŭkt). To draw backward or toward the back. [L. *dorsum*, back, + *duco*, pp. *ductus*, to draw]

dor·si·flex·ion (dōr-si-flek′shăn). Upward movement (extension) of the foot or toes or of the hand or fingers.

dor·si·scap·u·lar (dōr′si-skap′ū-lăr). Relating to the dorsal surface of the scapula.

dor·si·spi·nal (dōr′si-spī′năl). Relating to the vertebral column, especially to its dorsal aspect.

dor·so·ceph·a·lad (dōr′sō-sef′ă-lad). Toward the occiput, or back of the head. [L. *dorsum*, back, + G. *kephalē*, head, + L. *ad*, to]

dor·so·lat·er·al (dōr-sō-lat′er-ăl). Relating to the back and the side.

dor·so·lum·bar (dōr-sō-lŭm′bar). Referring to the back in the region of the lower thoracic and upper lumbar vertebrae.

dor·so·ven·tral (dōr-sō-ven′tral). In a direction from the dorsal to the ventral aspect.

dor·sum, gen. **dor·si,** pl. **dor·sa** (dōr′sŭm, -sī, -să) [TA]. **1.** The back of the body. **2.** The upper or posterior surface, or the back, of any part. SYN tergum. [L. back]

d. ephip′pii, SYN d. sellae.

d. of foot [TA], the back, or upper surface, of the foot. SYN d. pedis [TA].

d. of hand [TA], the back of the hand; surface of hand opposite the palm.

d. lin′guae [TA], SYN d. of tongue.

d. ma′nus [TA], SYN dorsum of *hand*.

d. na′si [TA], SYN d. of nose.

d. of nose [TA], the external ridge of the nose, looking forward and upward. SYN d. nasi [TA].

d. pe′dis [TA], SYN d. of foot.

d. of penis [TA], the aspect of the penis opposite to that of the urethra. SYN d. penis [TA].

d. pe′nis [TA], SYN d. of penis.

d. scap′ulae, the posterior surface of the scapula.

d. sel′lae [TA], a square portion of bone on the body of the sphenoid posterior to the sella turcica or hypophysial fossa. SYN d. ephippii.

d. of tongue [TA], the back of the tongue; the upper surface of the tongue divided by the sulcus terminalis into an anterior two-thirds, the pars presulcalis (presulcal part), and a posterior one-third, the pars postsulcalis (postsulcal part). SYN d. linguae [TA].

dos·age (dōs′ij). **1.** The giving of medicine or other therapeutic agent in prescribed amounts. **2.** The determination of the proper dose of a remedy. Cf. dose. **3.** In nuclear medicine, quantity of radiopharmaceutical given.

dose (dōs). **1.** The quantity of a drug or other remedy to be taken or applied all at one time or in fractional amounts within a given period. Cf. dosage (2). **2.** In nuclear medicine, amount of energy absorbed per unit mass of irradiated material (absorbed d.). SEE ALSO dosage (3). [G. *dosis*, a giving]

absorbed d., the amount of energy absorbed per unit mass of irradiated material at the target site; in radiation therapy, the former unit for absorbed d. is the rad (100 ergs/g); the current (SI) unit is the gray (1 J/kg or 100 rad).

air d., SYN exposure d.

bone marrow d., the cumulative d. to the blood-forming organ from therapeutic or nuclear fallout irradiation; the presumed leukemogenic d.

booster d., a d. given at some time after an initial d. to enhance the effect, said usually of antigens for the production of antibodies.

cumulative d., the total d. resulting from repeated exposures to radiation or chemotherapy of the same part of the body or of the whole body.

curative d. (CD, CD^{50}), (1) the quantity of any substance required to effect the cure of a disease or that will correct the manifestations of a deficiency of a particular factor in the diet; (2) effective d. used with therapeutically applied compounds. SEE ALSO CD^{50}. SYN therapeutic d.

daily d., the total amount of a remedy that is to be taken within 24 hours.

depth d., the d. of radiation at a distance beneath the surface, including secondary radiation or scatter, in proportion to the d. at the surface.

divided d., a definite fraction of a full d.; given repeatedly at short intervals so that the full d. is taken within a specified period, usually one day. SYN fractional d.

effective d. (ED), (1) the d. that produces a specific effect; when followed by a subscript (generally "ED_{50}"), it denotes the d.

p. gluconate, gluconic acid p. salt, used in hypokalemia as a replenisher.

p. guaiacolsulfonate, used as an expectorant.

p. hydroxide, KOH; a strong, penetrating caustic. SYN caustic potash.

p. hypophosphite, formerly believed to have a tonic effect upon the nervous system; may be explosive if triturated or heated with oxidizing agents.

p. iodate, an oxidizing agent and disinfectant.

p. iodide, KI; used as an alterative and expectorant, and in certain mycoses.

p. metaphosphate, a pharmaceutic aid (buffer).

monobasic p. phosphate, used as a urinary acidifier and buffer.

p. nitrate, sometimes used as a diuretic and diaphoretic; formerly it was included in asthmatic powders containing stramonium leaves. SYN niter, saltpeter.

penicillin G p., SEE *penicillin* G potassium.

p. perchlorate, occasionally used, as an alternative to a thiouracil derivative, in the control of hyperthyroidism.

p. permanganate, a strong oxidizing agent, used in solution as an antiseptic and deodorizing application for foul lesions, and formerly as a gastric lavage in poisoning from morphine, strychnine, aconite, and picrotoxin; in electron microscopy, it stains cytomembranes well and gives results similar to lead hydroxide staining; also used as a fixative (Luft).

p. phosphate, a mild saline cathartic and diuretic. SYN dibasic p. phosphate, dipotassium phosphate.

p. rhodanate, SYN p. thiocyanate.

p. sodium tartrate, a mild saline cathartic, used as an ingredient in compound effervescent powders. SYN Rochelle salt, Seignette salt, sodium potassium tartrate.

p. sorbate, 2,4-hexadienoic acid potassium salt; a mold and yeast inhibitor, used as a preservative.

p. succinate, a deliquescent powder used as a hemostatic.

p. sulfate, an obsolete laxative.

p. sulfocyanate, SYN p. thiocyanate.

p. tartrate, a mild purgative and diuretic. SYN soluble tartar.

p. thiocyanate, formerly used in the treatment of essential hypertension and as a reagent in the detection of copper, iron, and silver. SYN p. rhodanate, p. sulfocyanate.

potassium-39 (^{39}**K**). Most abundant, nonradioactive isotope of potassium; accounts for 93.1% of natural potassium.

po·tas·si·um-40 (^{40}**K**). A naturally occurring (0.0117%) radioactive potassium isotope; beta emitter with half-life of 1.26 billion years; chief source of natural radioactivity of living tissue.

po·tas·si·um-42 (^{42}**K**). An artificial potassium isotope; beta emitter with half-life of 12.36 hr, used as a tracer in studies of potassium distribution in body fluid compartments and in localization of brain tumors.

po·tas·si·um-43 (^{43}**K**). An artificial potassium isotope; a beta emitter with a half-life of 22.3 hr, used as a tracer in myocardial perfusion studies.

po·ten·cy (pō'ten-sē). **1.** Power, force, or strength; the condition or quality of being potent. **2.** Specifically, sexual p. **3.** In therapeutics, the relative pharmacologic activity of a dose of a compound compared with the dose of a different agent producing the same effects; e.g., aspirin and acetaminophen are of equal potency in alleviating headache (same dose required), but ketarolac exhibits greater potency than ibuprofen, as 20 mg of the former is as effective as 400 mg of the latter. [L. *potentia,* power]

sexual p., the ability to carry out and consummate sexual intercourse, usually referring to the male.

po·tent (pō'tent). **1.** Possessing force, power, strength. **2.** Indicating the ability of a primitive cell to differentiate. SEE ALSO totipotent, pluripotent, unipotent. **3.** In psychiatry, possessing sexual potency.

po·ten·tial (pō-ten'shăl). **1.** Capable of doing or being, although not yet doing or being; possible, but not actual. **2.** A state of tension in an electric source enabling it to do work under suitable conditions; in relation to electricity, p. is analogous to the temperature in relation to heat. [L. *potentia,* power, potency]

action p., the change in membrane p. occurring in nerve, muscle, or other excitable tissue when excitation occurs.

after-p., SEE afterpotential.

bioelectric p., electrical p.'s occurring in living organisms.

biotic p., a theoretical measurement of the capacity of a species to survive or to compete successfully.

brain p., the electrical charge of the brain as compared to a point on the body; the p. may be steady (DC p.) or may fluctuate at specific frequencies when recorded against time, giving rise to the electroencephalogram.

brainstem auditory evoked p., responses triggered by click stimuli, which are generated in the acoustic nerve and brainstem auditory pathways; recorded over the scalp.

chemical p. (μ), a measure of how the Gibbs free energy of a phase depends on any change in the composition of that phase.

cochlear p., SYN cochlear microphonic.

compound action p., the combined p.'s resulting from activation of the auditory division of the eighth cranial nerve.

demarcation p., the difference in p. recorded when one electrode is placed on intact nerve fibers or muscle fibers and the other electrode is placed on the injured ends of the same fibers; the intact portion is positive with reference to the injured portion. SYN injury p.

early receptor p. (ERP), a voltage arising across the eye from a charge displacement within photoreceptor pigment, in response to an intense flash of light.

endocochlear p., the standing direct current p. in the endolymph relative to the perilymph, measuring positive 80 mV.

evoked p., an event-related potential, elicited by, and time-locked to, a stimulus. SEE ALSO evoked *response.*

excitatory junction p. (EJP), discrete partial depolarization of smooth muscle produced by stimulation of excitatory nerves; similar to small end-plate p.'s. summate with repeated stimuli.

excitatory postsynaptic p. (EPSP), the change in p. that is produced in the membrane of the next neuron when an impulse that has an excitatory influence arrives at the synapse; it is a local change in the direction of depolarization; summation of these p.'s can lead to discharge of an impulse by the neuron.

generator p., local depolarization of the membrane p. at the end of a sensory neurone in graded response to the strength of a stimulus applied to the associated receptor organ, e.g., a pacinian corpuscle; if the generator p. becomes large enough (because the stimulus is at least of threshold strength), it causes excitation at the nearest node of Ranvier and a propagated action p.

inhibitory junction p. (IJP), hyperpolarization of smooth muscle produced by stimulation of inhibitory nerves.

inhibitory postsynaptic p. (IPSP), the change in p. produced in the membrane of the next neuron when an impulse that has an inhibitory influence arrives at the synapse; it is a local change in the direction of hyperpolarization; the frequency of discharge of a given neuron is determined by the extent to which impulses that lead to excitatory postsynaptic p.'s predominate over those that cause inhibitory postsynaptic p.'s.

injury p., SYN demarcation p.

membrane p., the p. inside a cell membrane, measured relative to the fluid just outside; it is negative under resting conditions and becomes positive during an action p. SYN transmembrane p.

myogenic p., action p. of muscle.

oscillatory p., the variable voltage in the positive deflection of the electroretinogram (β-wave) of the dark-adapted eye arising from amacrine cells.

Ottoson p., SYN electroolfactogram.

oxidation-reduction p. (E_h or E_h^*), the p. in volts of an inert metallic electrode measured in a system of an arbitrarily chosen ratio of [oxidant] to [reductant] and referred to the normal hydrogen electrode at absolute temperature; it is calculated from the following equation; where R is the gas constant expressed in electrical units, T the absolute temperature (Kelvin), n the number of electrons transferred, F the faraday, and E_0 the normal symbol for the p. of the system at pH 0; for biologic systems, E_0' is often used (in which pH = 7). Cf. Nernst *equation.* SYN redox p.

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Stereoselective pharmacokinetics of doxepin isomers

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Summary. Commercial preparations of the tricyclic antidepressant doxepin contain 15% of the more active cis-doxepin and 85% of the trans-isomer. The single dose pharmacokinetics of doxepin and its major metabolite N-desmethyldoxepin were examined in 30 healthy young men.

Results for total doxepin showed wide intersubject variation in all pharmacokinetic parameters except t_{max} and C_{max}. Plasma levels of cis-doxepin were extremely low and it was only possible to estimate the stereoselective pharmacokinetics of the parent drug in 3 subjects. The data from those particular subjects resulted in an average ratio of cis- to trans-doxepin isomers in plasma of 15:85.

In contrast, the mean plasma levels of cis-N-desmethyldoxepin in 28 subjects exceeded those of the trans-isomer at every time point after 10 h, such that the areas under the plasma concentration versus time curves (AUC) of cis-N-desmethyldoxepin were significantly higher than those of the corresponding trans-isomer. This phenomenón may play an important role in the therapeutic action of doxepin since it has been suggested that cis-N-desmethyldoxepin is pharmacologically active. In 2 subjects, however, the AUC 0-inf of trans-N-desmethyldoxepin were respectively 4 and 8 fold higher than those of the cis-isomer.

Key words: Doxepin; N-desmethyldoxepin, stereoselective pharmacokinetics, stereoselective metabolism, Cis isomer, trans isomer

Doxepin is a tricyclic antidepressant which is marketed as a mixture of geometric isomers in a cis:trans ratio of 15:85, although animal studies suggest that the cis-isomer may be the more active [1]. A review of the literature reveals that few studies have been carried out on the pharmacokinetics of doxepin in humans, primarily because of analytical difficulties caused by low plasma or serum concentrations. For this reason, the majority of studies have been carried out in patients at steady state, although low plasma or serum concentrations may still be a concern, even in patients receiving moderately high doses of 100 to 200 mg daily [2].

The fact that the drug is marketed as an irrational mixture of geometric isomers adds to the difficulties in carrying out and interpreting pharmacokinetic studies. Rosseel and co-workers [3] reported that the plasma levels of cis- and trans-doxepin in two patients were approximately in the same ratio as that in the dosage form administered (15:85), although the plasma levels of cis-N-desmethyldoxepin were clearly higher relative to those of the trans-isomer. Hrdina and co-workers [4] also found evidence of higher plasma levels of cis-N-desmethyldoxepin relative to those of the trans-isomer. Recently it was shown that both aromatic hydroxylation and glucuronidation are involved in the metabolism of N-desmethyldoxepin [5]. Unfortunately, there is insufficient quantitative evidence by which to judge the importance of these metabolic pathways in the pharmacokinetics of N-desmethyldoxepin.

In a recent study, Ghabrial and co-workers [6] administered to 8 volunteers, a mixture of 25 mg of cis-doxepin and 25 mg deuterium labelled trans-doxepin. There was no apparent interconversion between the isomers of doxepin although there was evidence of stereoselective excretion. Moreover, significant amounts of cis-N-desmethyldoxepin were formed after the administration of trans-doxepin. The N-desmethyl metabolite is known to be pharmacologically active and it has even been suggested that the total concentration of cis- plus trans-doxepin and N-desmethyldoxepin in plasma may show better correlation with antidepressant effects than the parent drug alone [7]. Several other studies have also included correlations between clinical effect and plasma or serum concentrations of the N-desmethyl metabolite concentrations [8–10]. Thus it is possible that any enrichment of cis-N-desmethyldoxepin may have therapeutic significance.

The single dose pharmacokinetic studies on total doxepin that have been published to date [11–13] report that doxepin was rapidly absorbed from the gastrointestinal tract with maximum (cis- plus trans-) plasma concentrations (C_{max}) occurring approximately 2 h after adminis-

tration. The drug has a high hepatic extraction ratio. At present it is not known whether the metabolism of doxepin in vivo is related to debrisoquine hydroxylase. Plasma concentrations of (cis- plus trans-) N-desmethyldoxepin appeared to peak later and at lower levels that those of the parent drug, but with a greater area under the plasma concentration versus time curve (AUC). The present report describes the first single dose study to address stereoselective aspects of the pharmacokinetics of doxepin and its important metabolite N-desmethyldoxepin after the administration of the standard dosage form containing 15% cis-doxepin and 85% trans-doxepin.

Materials and methods

Subjects

The subjects were selected from a cohort of healthy male caucasian volunteers, aged 18–45 y, and deviating by no more than ± 10% from the ideal weight for height according to the Metropolitan Life Insurance Company Bulletin, 1983. Each subject was required to be free of cardiovascular, hepatic, renal, or gastrointestinal diseases, drug abuse or alcohol dependence, as assessed by physical examination and review of medical history. In addition, the blood pressure, electrocardiogram and results of clinical laboratory tests (blood chemistry, haematology and urinalysis) were required to be within normal ranges. Of the subjects who met the entry requirements, 30 completed the study. All subjects were required to abstain from the use of all other drugs (including non-prescription drugs) for at least 1 week prior to and until after completion of the study. The subjects were also required to refrain from consuming alcoholic or caffeine containing beverages from 48 h prior to dosing until after the collection of the last blood sample.

Study design

All volunteers gave informed consent before participating in the study. The study protocol was approved by the local institutional review board. Each subject consumed three capsules containing 25 mg doxepin hydrochloride (Sinequin®, Roerig). Blood samples (15 ml) were drawn in heparinised evacuated tubes, immediately before dosing, and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0 and 24 h after dosing. Blood samples were also collected on days 2, 3, 4, 5 and 7. Care was taken to ensure that the blood did not come into contact with the rubber stopper at any time during the collection procedure. Within 30 min of collection, each blood samples was centrifuged to separate plasma which was then divided into two aliquots and frozen (− 20°C) until analysis.

Analysis of plasma samples

Each sample of plasma (2 ml) was pipetted into a disposable glass tube (15 ml) to which was added 1 ml of an aqueous solution containing the internal standards (imipramine, 3 ng·ml^{-1}, for doxepin analysis; and maprotiline, 500 ng·ml^{-1}, for N-desmethyldoxepin analysis). The tube was shaken for 5 s (vortex mixer) before the addition of 1 ml of a saturated solution of sodium carbonate. After shaking (5 s, vortex mixer), n-pentane (10 ml) was added, the tube was stoppered and shaken for 15 min (vortex mixer). The tube was then allowed to stand for 2 min to allow the layers to separate after which the organic layer was transferred to a clean 12 ml disposable glass tube. Pentafluorobenzoylchloride (PFBC, 100 µl 0.005% in pentane) was added to form pentafluorobenzamide derivatives of N-desmethyldoxepin and maprotiline for sensitive analysis by means of the electron capture detector (ECD). The tube was stoppered and the contents incubated for an hour at 50°C (Dri-bath). After cooling, 0.5 ml 0.1 M ammonia solution was added and the mixture shaken for 5 min (vortex mixer). The tube was then allowed to stand for 2 min for the layers to separate. The organic layer was divided into two aliquots for analyses of doxepin and N-desmethyldoxepin.

To the aliquot for doxepin analysis was added isopropanol (100 µl) and an anti-bumping granule. The solvents were then evaporated at 65°C (Dri-bath) and the residue allowed to cool before the addition of 30 µl acetonitrile. After mixing (vortex), the reconstituted extract (20 µl) was injected into the high performance liquid chromatograph (HPLC).

To the aliquot of organic extract set aside for N-desmethyldoxepin analysis was added an anti-bumping granule and the solvent was evaporated at 65°C (Dri-bath). After cooling, the residue was reconstituted in ethyl acetate (20 µl), 1.5 µl aliquots of which were injected into the GLC.

The HPLC analysis of total doxepin (HPLC Method A) was carried out with the following equipment: a Waters Model 590 HPLC pump; a Rheodyne Injector Model 7125; a Spherisorb CN column (3 µm, 4.6 × 150 mm); an ESA Coulochem detector Model 5100A with Model 5011 high sensitivity analytical cell (Det.1 potential 0.65 V, Det. 2 potential 0.85 V and a guard cell potential of 1.00 V); a Terochem Dual pen recorder. The mobile phase consisted of 10% 0.1 M ammonium acetate and 10% methanol in acetonitrile. The flow rate was 1.5 ml·min^{-1}.

The stereoselective HPLC analysis of doxepin (HPLC Method B) was carried out with the same equipment described above except that the detector was a Waters Model 481 UV detector operated at 254 nm and the column was a Zorbax Sil (4.6 × 250 mm) column. The mobile phase consisted of 1% methylene chloride, 1% methanol, and 0.01% diethylamine in n-hexane.

The stereoselective GLC analysis of N-desmethyldoxepin was carried out with the following equipment: a Hewlett Packard Model 5890 gas-liquid chromatograph with the injector temperature set at 300°C and the column oven set to operate at 265°C for 1 min and thereafter to rise by 10°/min to a final temperature of 295°C; a DB225 fused silica capillary column (0.32 mm × 25 meters); a ^{63}Ni ECD operated at 350°C and a make up gas of 10% argon in methane with a flow rate of 30 ml·min^{-1}. The carrier gas was 10% argon in methane. The flow rate was 1.5 ml·min^{-1} with a corresponding head pressure of 7 psi and an infection purge time of 0.2 min.

Standard curves were run daily with each of the analytical methods described above. Quality control (QC) samples, prepared by adding known amounts of the appropriate analytes to blank plasma, were analyzed (analyst blind) along with the test samples each day. Analytical data for any day were rejected if the mean difference between the amount spiked and the amount determined exceeded ± 15% in more than 2 out of 6 QC samples.

Reference samples of cis- and trans-doxepin, trans-N-desmethyldoxepin and doxepin N-oxide were kindly donated by Pfizer Inc. (Groton Con). A reference sample of cis-N-desmethyldoxepin was isolated from the urine of patients under medication with doxepin and characterised as described previously [5]. All commercially available chemicals were of analytical grade and the solvents were HPLC grade.

Analysis of data and statistics

Pharmacokinetic parameters for doxepin and N-desmethyldoxepin were determined by standard techniques. The maximum plasma concentration (C_{max}) and time to reach maximum plasma concentration (t_{max}) were obtained directly from the plasma concentration versus time curve. The area under the plasma concentration versus time curve up to the last time (t_{last}) showing a measurable concentration (C_{last}) of each analyte [AUC(0-t)], was determined by means of the

Table 1. Ty

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Table 1. Typical standard curves ($y = ax^2 + bx + c$)

Analyte	Method	Range ng·ml^{-1}	Constant a	Slope b	Intercept c	r^2	Composite [a]CV %
Total doxepin	HPLC/A	[b]0.25–25.0	0	0.2084	+ 0.0219	0.9999	5.17
Cis-doxepin	HPLC/B	[b]2.5–100.0	0	0.0341	−0.0173	0.9968	10.21
trans-doxepin	HPLC/B	[b]2.5–100.0	0	0.0107	+ 0.0126	0.9999	8.53
Cis-N-desmethyldoxepin	GLC	[b]0.3–7.5	0.0126	0.4848	−0.0019	0.9996	3.36
Trans-N-desmethyldoxepin	GLC	[b]0.3–7.5	0.0002	0.3291	+ 0.0275	0.9998	3.71

At least four data points contributed to each standard curve. Each datum point was the mean of at least 3 measurements.
[a] Calculated as the mean of the CVs at each concentration on the standard curve.
[b] The lowest concentration of the range was considered to be the limit of quantitation

Table 2. Pharmacokinetics of total doxepin and cis- and trans-N-desmethyldoxepin in 30 men

	C_{max} ng·ml^{-1}	t_{max} hr	k	$t_{1/2}$ hr	AUC(0-t) ng·h·ml^{-1}	AUC ng·h·ml^{-1}
Total doxepin	13.6 (7.7)	2.53 (1.3)	0.0605 (39.5)	13.2 (38.6)	169 (78.7)	180 (74.1)
Cis-N-desmethyldoxepin	2.29 (22.4)	11.3 (81.4)	0.0285[a] (48.1)	31.8[a] (61.1)	104 (31.8)	113[a] (33.6)
Trans-N-desmethyldoxepin	2.83 (53.4)	4.58 (122)	0.0665 (54.0)	14.9 (82.4)	85.7 (200)	96.6 (205)

The figures in parentheses are percentage coefficients of variation.
[a] Data from the two outliers included ($n = 29$)

linear trapezoidal rule for ascending and log trapezoidal rule for descending portions of the curve. A rate constant was calculated by least squares regression of the natural logs of the last three plasma concentrations.

AUC(0-inf) values (AUC) were determined by adding to the appropriate AUC(0-t), the quotient of C_{last} and the appropriate value of k. A half-life value was calculated from the quotient of ln2 and k.

Results

Doxepin N-oxide is known to be a metabolite of doxepin in both humans [5, 14] and animals [15]. It has been reported that tertiary amine N-oxides may undergo reduction to the tertiary amine during extraction from plasma made alkaline with sodium hydroxide, resulting in spuriously high plasma levels of the parent drug [16]. In order to establish the lability of doxepin N-oxide under analytical conditions, a total of 25 plasma samples from 3 different subjects were analyzed after extraction from aliquots of plasma made alkaline with either sodium carbonate (pH 11.6) or sodium hydroxide (pH 13.6). All plasma samples were subjected to an extraction procedure with two aliquots of organic solvent which was reported to aggravate the problem [16]. The results showed that doxepin levels in samples made alkaline with sodium hydroxide were, on the average, 138.6% (SD 50.0%) higher than in samples made alkaline with sodium carbonate. A Student's t-test ($t = 3.848 > t_\alpha = 3.745$ with $n - 1 = 24$ df and $\alpha = 0.0005$ in one tail) indicated that doxepin levels were significantly higher in plasma samples made alkaline with sodium hydroxide. Further tests, in which synthetic doxepin N-oxide was added to blank human plasma, showed that there was no detectable production of doxepin during extraction under the conditions employed in the present pharmacokinetic study.

Some typical standard curves are described in Table 1. The precision and accuracy of the analytical procedures under field conditions were determined from the results of blind QC samples run on each day of analysis. Completion of the study took approximately 2 months with 30 individual analytical runs. In excess of 180 blind QC samples were analysed over this period. Over this time course, the HPLC analysis for total doxepin displayed a mean percentage difference (SD) between the nominal and observed concentrations of the QCs of 4.5 (5.9)%, 6.9 (4.6)% and 11.0 (9.2)% at 15, 7.5 and 1.25 ng·ml^{-1}, respectively. The relatively low percentage difference between the nominal and observed concentrations attests to the accuracy of the procedure while the low standard deviations at each concentration attests to the precision. Similar studies were carried out with the GLC procedure for trans-N-desmethyldoxepin, in which the mean percentage differences (SD) between nominal and observed concentrations of the QCs were 7.8 (5.2)%, 8.6 (5.1)% and 7.3 (5.9)% at 3.6, 1.8 and 0.9 ng·ml^{-1}, respectively. Unfortunately, insufficient supplies of cis-N-desmethyldoxepin were available to permit the preparation of daily QC samples. Note, however, that standard curve data (Table 1) showed that the cumulative mean % CV for cis-N-desmethyldoxepin (3.36%) was similar to that of the trans-isomer (3.71%), which suggests that the two assays were comparable.

The lower limit of quantitation of cis- or trans-doxepin by HPLC method B was 2.5 ng·ml^{-1} which was not low enough to permit the use of HPLC method B in single dose pharmacokinetic studies. HPLC Method B was used, however, to examine the concentrations of cis- and

an important step in the understanding of the pharmacokinetic basis of the therapeutic action of doxepin in the treatment of depression, since it has been reported that cis-N-desmethyldoxepin is pharmacologically active [1]. Moreover, the two outliers (subjects 6 and 18) clearly exhibited different pharmacokinetic characteristics from the majority of subjects in the study.

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United States Patent [19]

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[11] Patent Number: 5,502,047

[45] Date of Patent: Mar. 26, 1996

[54] **TREATMENT FOR INSOMNIA**

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[52] U.S. Cl. **514/183**; 514/923; 514/450; 514/453

[58] Field of Search 514/923, 450, 514/453, 183

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[57] ABSTRACT

A method for the treatment of chronic insomnia is disclosed which involves the administration of low dosages of a compound selected from the pharmaceutically acceptable forms of doxepin, trimipramine, amitriptyline, trazodone and mixtures hereof.

10 Claims, No Drawings

TREATMENT FOR INSOMNIA

FIELD OF INVENTION

This invention relates to a method for the treatment of individuals suffering from chronic insomnia. In a preferred embodiment, the present invention relates to a method for the treatment of chronic insomnia in individuals other than those suffering from depression.

BACKGROUND OF THE INVENTION

A large percentage of the adult population suffers from insomnia in some form at some time in their lives. This may vary from an occasional episode to chronic conditions and may involve onset and/or maintenance insomnia. Chronic insomnia is typically accepted to involve episodes greater than three (3) weeks in duration. The effects of sleep deprivation resulting from such insomnia are well known and need not be described herein other than to say that they are to be avoided.

Currently, there exist treatments only for acute insomnia. These treatments involve the administration of medication, either of the non-barbiturate or barbiturate type, shortly before bedtime. While both types of sedatives may be used to effectively treat insomnia, neither is without its undesirable side effects. For instance, barbiturate type sedatives, such as secobarbital sodium (sold by Eli Lilly and Company under the tradename of Seconal®) are general depressants. While effective, these medications are well known to lose their effectiveness after a few days. They are further highly addictive and commonly abused. They are thereforc no longer widely prescribed.

The group of medications now most commonly used for the treatment of insomnia are the benzodiazepines. There are now 5 such "hypnotics" commonly used. They differ significantly in half lives but are otherwise very similar and equally effective. They have supplanted the barbiturates as the principal treatment for insomnia because they have slightly less addiction potential and are associated with less risk for suicide than the barbiturates unless taken with alcohol. However, this group, too, is know to be effective only for acute or short term insomnia and the medications are not acceptedly used for chronic insomnia. Furthermore, they are also addictive and their wide usage is drawing increasing concern as their potential side effects become more apparent. These include daytime sedation, decreased cognitive abilities such as memory loss and, most recently in the case of Halcion®(triazolam), agitated behavior.

The present invention involves the administration of very small doses of specific known psychotherapeutic agents. These agents include tricyclic compounds and a triazolopyridine derivative which are currently prescribed both for the general treatment of depression and for the treatment of the insomnia component of a depression in individuals suffering from severe depression. These compounds are known to possess a sedative effect in such individuals when administered in moderate to large dosages. However, the use of these compounds at the extremely low dosages claimed herein for the successful treatment of chronic insomnia in otherwise healthy individuals has not been reported and is not obvious in view thereof. For example, the compounds used in the present invention are currently prescribed for a 20–60 year old depressed patient population in dosages varying from about 75 to about 300 milligrams per day of the tricyclic compounds and about 150 to about 600 milligrams per day of the triazolopyridine compound. The entire dosage of such medications are often administered at bedtime. In contrast, the method of the present invention involves the use of a small fraction of such dosage.

OBJECTS OF THE INVENTION

It is an object of the present invention to develop a method for the successful treatment of chronic insomnia.

It is another object of the present invention to develop a method for the successful treatment of insomnia in individuals not suffering from depression.

It is still another object of the present invention to develop a method for the treatment of chronic insomnia using non-addictive medications.

It is a further object of the present invention to develop a method for the treatment of chronic insomnia which does not involve the adverse effects associated with the currently prescribed hypnotics, i.e. residual sedation, lethargy, drowsiness, loss of cognitive ability and/or agitation.

SUMMARY OF THE INVENTION

The present invention is directed to a method for the treatment of a patient suffering from chronic insomnia comprising administering to said patient a compound selected from the group consisting of the pharmaceutically acceptable forms of doxepin, amitriptyline, trimipramine, trazodone and mixtures thereof. The dosage for administration of doxepin, amitriptyline, trazodone, trimipramine and mixtures thereof ranges from about 0.5 to about 20.0 milligrams.

In one preferred embodiment of the present invention, the invention is directed to a method for the treatment of a patient suffering from chronic insomnia comprising administering to said patient doxepin, amitriptyline, trimipramine or mixtures thereof in a dosage of about 10 milligrams or less.

In another preferred embodiment of the present invention, the invention is directed to a method for the treatment of a patient suffering from chronic insomnia comprising administering to said patient trazodone in a dosage of about 15 milligrams or less.

In yet another embodiment, the present invention is directed to a method for the treatment of chronic insomnia in a patient who is not suffering from depression comprising administering to said patient a compound selected from the group consisting of the pharmaceutically acceptable forms of doxepin, amitriptyline, trimipramine, trazodone and mixtures thereof in a dosage ranging from about 0.5 to about 20 milligrams.

DESCRIPTION OF THE INVENTION

The method of the present invention involves the administration of doxepin, amitriptyline, trimipramine, trazodone and mixtures thereof. As noted above, these compounds are well known psychotherapeutic agents which are currently prescribed as antidepressants. Each compound is further readily available commercially. The hydrochloride salt of doxepin is currently marketed by Pfizer Inc. under the tradename Sinequan®. The hydrochloride salt of amitriptyline is currently marketed by Merck & Co., Inc. under the tradename Elavil®. Trimipramine maleate is currenly marketed by Wyeth-Ayerst Laboratories under the tradename Surmontil®. The hydrochloride salt of trazodone is currently marketed by Mead Johnson Pharmaceuticals under the tradename Desyrel®.

Of the above compounds which are commercially available as a hydrochloride salt or a malcatc in the case of trimipramene, it should be understood that the use of other pharmaceutical salts of such compounds are also within the practice of the present invention. Furthermore, although the above compounds are commercially available in various forms, use of these compounds in other than currently

administratable forms (e.g. injectable solutions, capsules, caplets) is also within the scope of the present invention.

As stated above, dosages of doxepin, amitriptyline, trimipramine or mixtures thereof may vary from about 0.5 to about 20.0 milligrams. Preferably dosages of about 10 milligrams or less are utilized. Most preferably, dosages of about 5 milligrams or less are utilized. With respect to trazodone, dosages of about 0.5 to about 20 milligrams are used. Preferably, dosages of about 15 milligrams or less are used. However, as it is recognized that each individual may react differently to a given dose of the medication used herein, the dosages recited herein should be accorded flexibility. Since the point of the present invention is to induce and maintain normal sleep without exposing the patient to residual effect of medication, the lowest effective dosage of the compounds are to be utilized whenever possible.

Administration of the compounds should take place within about one hour before bedtime. Again, the onset of the sedative effect will vary with the individual and the dosage prescribed.

"Depression" as used herein refers to a psychiatric diagnosis of depression and includes those disorders categorized under depression in the Psychiatric Diagnostic and Statistical Manual 3, American Psychiatric Association Press.

The following Examples are offered to illustrate the claimed method and its practice. They should not however be construed in any way as a limitation to the scope of the present invention.

EXAMPLE 1

The patient was a thirty-eight year old female who suffered from maintenance insomnia for one year. She had been treated previously with "hypnotics" and, at the time of presentation, was using diphenhydramine 50–100 mg hs without success. Psychotherapy had also failed to relieve the insomnia. At the time of consultation, she had normal affect with no depression, anxiety or substance overuse. She was started on doxepin 10 mg hs. Follow up at 30 days revealed her to be sleeping well. An attempt to decrease the dosage produced a return of the insomnia. She is currently maintained on 10 mg of doxepin and is doing well.

EXAMPLE 2

The patient was a fifty-two year old female with a maintenance insomnia of three years' duration. She had tried several therapeutic modalities including dalmane 15 mg hs, hypnosis, and a behavioral program all without improvement. At the time of presentation, affect was normal and there was no depression or anxicty. Alcohol use was not a factor. She was prescribed doxepin 5 mg hs which produced an immediate resolution of the disturbed sleep. The doxepin was subsequently discontinued and the insomnia returned. She was restarted on doxepin at 5 mg hs and the insomnia again was relieved. Maintenance is ongoing at this dosage.

EXAMPLE 3

The patient was a fifty-two year old male with a long-standing maintenance insomnia. He had been treated with temazepam 15 mg hs for many years but was suffering memory loss and had a fear of addiction. Clinical evaluation revealed normal affect without depression, anxiety, or substance use. He was started on doxepin 10 mg hs which rapidly restored sound, uninterrupted sleep. An attempt to lower the dosage ended with a return of the insomnia. The dosage level was increased back to 10 mg with resolution of the sleep disturbance. He is currently maintained at that dosage and is doing well.

EXAMPLE 4

The patient was a forty-nine year old female with a maintenance insomnia of two years' duration. She had previously been treated with diazepam for anxiety and the insomnia with no effect on the latter. She had a past history of depression but had normal affect and no depression at her initial consultation or during her treatment. Alcohol use was not significant. She was started on doxepin 12.5 mg hs upon which the insomnia was resolved. At long term follow up there was no sleep complaint at this dosage.

EXAMPLE 5

The patient was a sixty-five year old male retiree with an onset and maintenance insomnia of thirty years' duration. He had attempted self-treatment unsuccessfully with several over-the-counter preparations. Prescription "sleeping pills" has been similarly ineffective. At the time of presentation, the patient had a normal affect with no anxiety, depression, or substance abuse. Therapy was initiated with doxepin 10 mg hs which effected undisturbed and restful sleep. He is now maintained on doxepin 8 mg hs and is doing well.

EXAMPLE 6

The patient was a fifty-four year old male who had developed a maintenance insomnia. He had been previously treated with alprazolam 0,125 mg hs without improvement. A behavioral program combined with attempted withdrawal from the alprazolam was ineffective. Clinical evaluation revealed a normal affect and mental status, and an absence of depression, anxiety and substance abuse. He was started on doxepin 5 mg hs which produced a clinical cure. After two years at this dosage, he continues to sleep well and has experienced no adverse effects from the medication.

I claim:

1. A method for the treatment of a patient suffering from chronic insomnia comprising administering to said patient a compound selected from the group consisting of doxepin and pharmaceutically acceptable salts thereof in a daily dosage ranging from about 0.5 to about 20 milligrams.

2. The method of claim **1** wherein the pharmaceutically acceptable salt of doxepin is the hydrochloride salt thereof.

3. The method of claim **1** where the daily dosage is about 0.5 to about 10 milligrams.

4. The method of claim **1** where the daily dosage is about 0.5 to about 5 milligrams.

5. The method of claim **2** where the daily dosage is about 0.5 to about 10 milligrams.

6. The method of claim **2** where the daily dosage is about 0.5 to about 5 milligrams.

7. The method of claim **1** wherein the patient is suffering from depression.

8. The method of claim **1** wherein the patient is suffering from depression.

9. The method of claim **4** wherein the patient is not suffering from depression.

10. The method of claim **5** wherein the patient is not suffering from depression.

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(12) EX PARTE REEXAMINATION CERTIFICATE (5318th)

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Kavey

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(54) TREATMENT FOR INSOMNIA

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Primary Examiner—Shengjun Wang

(57) ABSTRACT

A method for the treatment of chronic insomnia is disclosed which involves the administration of low dosages of a compound selected from the pharmaceutically acceptable forms of doxepin, trimipramine, amitriptyline, trazodone and mixtures hereof.

EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims 1–7, 9 and 10 are cancelled.

Claim 8 is determined to be patentable as amended.

New claims 11–25 are added and determined to be patentable.

8. [The method of claim 1] *A method for the treatment of a patient suffering from chronic insomnia comprising administering to said patient a compound selected from the group consisting of doxepin and pharmaceutically acceptable salts thereof in a daily dosage ranging from about 0.5 to about 20 milligrams* wherein the patient is suffering from depression *and the insomnia is a component of the depression.*

11. The method of claim 8 wherein the daily dosage is about 0.5 to about 9 milligrams.

12. The method of claim 8 wherein the daily dosage is about 0.5 to about 4 milligrams.

13. A method for the treatment of a patient suffering from chronic insomnia comprising administering to said patient a compound selected from the group consisting of doxepin and pharmaceutically acceptable salts thereof in a daily dosage ranging from about 0.5 to about 20 milligrams wherein the patient is otherwise healthy.

14. The method of claim 13 wherein the daily dosage is about 0.5 to about 10 milligrams.

15. The method of claim 13 wherein the daily dosage is about 0.5 to about 5 milligrams.

16. The method of claim 13 wherein the daily dosage is about 0.5 to about 9 milligrams.

17. The method of claim 13 wherein the daily dosage is about 0.5 to about 4 milligrams.

18. The method of claim 13 wherein the daily dosage is about 3 milligrams.

19. A method for the treatment of a patient suffering from chronic insomnia comprising administering to said patient a compound selected from the group consisting of doxepin and pharmaceutically acceptable salts thereof in a daily dosage ranging from about 0.5 to about 4 milligrams.

20. The method of claim 19 wherein the daily dosage is about 0.5 to about 3 milligrams.

21. The method of claim 19 wherein the daily dosage is about 0.5 to about 2.5 milligrams.

22. The method of claim 19 wherein the daily dosage is about 0.5 to about 2 milligrams.

23. The method of claim 19 wherein the pharmaceutically acceptable salt of doxepin is the hydrochloride salt thereof.

24. The method of claim 19 wherein the patient is not suffering from depression.

25. The method of claim 19 wherein the patient is suffering from depression.

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